PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference XXX	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IN2004/000142	International filing date *(day/month/year)* 20.05.2004	Priority date *(day/month/year)* 19.03.2004
International Patent Classification (IPC) or national classification and IPC INV. C07H1/06 C07H5/02		
Applicant PHARMED MEDICARE PRIVATE LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 43 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.10.2005	17.07.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer de Nooy, A Telephone No. +31 70 340-2338

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000142

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-23	as originally filed
Claims, Numbers	
1-23	as originally filed
24, 25	received on 03.11.2005 with letter of 18.10.2005
Drawings, Sheets	
1-6	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☒ the description, pages 1-27
   - ☒ the claims, Nos. 26-31
   - ☒ the drawings, sheets/figs 7,8
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	24,25
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	24,25
Industrial applicability (IA)	Yes:	Claims	1-25
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

Amended claims 24 and 25 are considered allowable since in the original description (page 4 lines 9-16, page 23 lines 11-14) it is explicitly stated that the products from the process be amorphous or non-crystalline.
All other amendments however, being page 7 the description of the two extra figures, the extra material of pages 23-26, new claims 26-31 and new figures 7 and 8 are considered not-allowable (Rule 70.2(c) PCT) since in the original application there is no basis for those amendments. There can be no basis for new figures since those figures cannot be exactly the same as a text, therefore, the content of those figures cannot have been present in the original application. The new added pages as well as the new claims 26-31 are also considered to extent the scope of the original application because the addition of particle sizes was not present at all (only one remark, page 23 line 14) where it is stated that the powders have smaller particle size. However, no numbers are specified, therefore, any added number is considered unallowable added matter.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1: P.H. Fairclough et al. Carbohydrate Res. 40 (1975) 285-298
D2: US4380476

Novelty
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of newly filed claims 24 and 25 is not new in the sense of Article 33(2) PCT.

The documents D1 and D2 disclose the synthesis and isolation of sucralose, thus claims 24 and 25 lack novelty since a product by process must be new and inventive. A product is not rendered novel merely by the fact that it is produced by a new process. Moreover, both D1 and D2 disclose non crystalline sucralose (D1 page 293, sucralose was obtained as a syrup; D2 column 10 line 14 as a syrup) therefore, claims 24 and 25 are considered not

novel.

Inventive step
The present claims 1-23 meet the criteria of Article 33(1) PCT in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1-23, and discloses the synthesis and isolation of sucralose

The subject-matter of claims 1-23 differs from this known subject matter in that a drying step or super critical extraction step as in claim 1 is included. Furthermore, a deacetylation of intermediates of chlorinated sucrose is performed before as well as after said drying step.

The problem to be solved by the present invention may therefore be regarded as the provision of further processes for the synthesis and isolation of sucralose.

The solution proposed in claims 1-23 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons.
It is not obvious for the skilled person to include a drying step as in claim 1 and to perform a deacetylation before as well as after said drying step. In D1 there is no incentive to do so.

CLAIMS

1. A process of handling solution of sucrose intermediates and derivatives, including, chlorinated sucrose, comprising:

a) removal of liquids from the said solution by direct drying, under conditions mild enough to prevent degradation or modification of chlorinated sucrose, for recovery of solids from the said liquids and the end product of such operations is a solid mass of the chemicals visibly free from the said liquid;

b) recovering the said solids, present in the said liquid either in substantially pure form or with other solid impurities;

c) the said liquids being obtained in a process of producing chlorinated sucrose, mainly 1',6' Dichloro-1',6'-Dideoxy-â- D-Fructo-Furanosyl-4-Chloro-4-Deoxy-á-D-Galactopyranoside;

the said method of drying including one or a combination of, agitated thin film drying, spray drying, freeze drying and super critical extraction.

wherein the process of production of chlorinated sucrose comprises of,

i) deacylation of intermediates of chlorinated sucrose before as well as after drying of the chlorination reaction mixture by mild drying methods described above;

ii) use of alkali metal oxides as well as alkoxides, including Potassium Methoxide or Sodium Methoxide, for deacylation;

iii) achieving deacylation up to pH of 9 but well below pH 11.

2. The process of claim 1, wherein the chlorinated sucrose (or its intermediates or derivatives) containing liquid is a mixture of the respective substantially pure forms as well as of several solid ingredients of other chemicals in dissolved or suspended state.

3. The process of claim no. 2 wherein the individual ingredients of the said mixture of solids, containing chlorinated sucrose (or its intermediates or derivatives) as one of the ingredients, originate from reactants of a process undertaken for chlorination of sucrose-6-esters.

4. The process of claim no. 3 wherein the sucrose-6-ester is sucrose-6-acetate or sucrose-6-benzoate.

5. The process of claim no. 4 wherein the chlorinating reagent is any one suitable for chlorinating sucrose-6-ester.

6. The process of claim 5 wherein the said chlorinating reagent is a Vilsmeier reagent of the formula [XCIC.dbd.NR.sub.2].sup.+Cl.sup.- (where R represents an alkyl groupand X represents a hydrogen atom or a methyl group].

7. The process of claim no. 3 wherein in the said process of chlorination, sequence of steps involves addition of sucrose-6-ester solution in a tertiary amide to the chlorinating reagent for chlorination.

8. The process of claim no. 7 wherein the said tertiary amide is N, N-dialkylformamide.

9. The process of claim no. 8 wherein the said N, N-dialkylformamide is dimethylformamide.

10. The process of claim 1, wherein the chlorinated sucrose containing liquid contains chlorinated sucrose in pure form with impurities in small or trace quantities.

11. The process of claim 10 wherein the said chlorinated sucrose containing liquid, is a wash solvent collected as effluent from a column chromatography of an impure solution of chlorinated sucrose.

12. The process of claim 11 wherein the said wash solvent is subjected to concentration before subjecting to drying treatment.

13. The process of claim 11 wherein the said wash solvent used for desorbtion is either a single solvent like ethyl acetate, or mixture of solvents like mixture of toluene and methanol or mixture of methanol or water & ethyl acetate.

AMENDED SHEET

14. The process of claim no. 11 when the said column chromatography is done by using a suitable adsorbent preferably, alumina or silica gel.

15. The process of claim 11 when the said impure solution is the crude extract of chlorinated sucrose (or its intermediates or derivatives) from a solid powder mixture of several chemicals, including chlorinated sucrose; extraction being done by any suitable extraction process including supercritical extraction or by conventional extraction in any suitable solvent including water, ethyl acetate, methanol, methyl ethyl ketone, acetone, which are capable of selective extraction of substantially pure form of chlorinated sucrose free from impurities.

16. The process of claim no 15 wherein the said solid powder mixture is the product of process of drying of reaction mixture as described in claim nos. 3 to 12.

17. The process of claim 12 wherein the concentrated extract is subjected to conventional crystallization for purification of chlorinated sugar.

18. The process of claim 3, wherein the said process of chlorination comprises of:

i) preparation of Vilsmeir reagent from Phosphorus oxy-chloride,

ii) addition of sucrose-6-ester, preferably sucrose-6-acetate, to Vilsmeier reagent at 5.degree.to 10.degree.C. and allowing reaction to complete,

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iii) heating the reaction mixture to 80.degree.to100.degree.C., preferably between 90.degree.to 95.degree.C. and maintained for half to one hour,

iv) raising temperature of reaction mixture of step no. (iii) to 110.degree.C., preferably to 120.degree.to 130.degree.C. and maintained for 3-5 hours,

v) cooling the reaction mass to room temperature, cooling the reaction mass into a solution of a suitable deacylating reagent in inorganic basic solution like alkali hydroxide solution accompanied by further cooling to keep the temperature below 30.degree.to 35.degree.C.,

vi) adjusting the pH to 7 to 9.5 and preferably 8-9.

19. The process of claim18 wherein at step no. v), wherein any alkoxide, preferably Potassium Methoxide or Sodium Methoxide is used instead of alkali metal oxides for deacylation..

20. The process of claim no. 18 wherein pH is adjusted only upto 9 and reaction mixture is subjected to drying as per claim 1.

21. The process of claim 1 wherein the solids obtained from drying of reaction mixture from chlorination step are extracted for chlorinated sucrose recovery by any suitable method of extraction, including, solvent extraction.

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22. The process of claim 11 wherein the said impure solution is the solution of the solid powder mixture of several chemicals, including chlorinated sucrose, made in water and subjected to purification by application of separation methods including column chromatography, extraction in water immiscible solvent having selective affinity with chlorinated sucrose or chlorinated sucrose intermediates or chlorinated sucrose derivatives

23. The process of claim 11 when the said impure solution is the crude extract of chlorinated sucrose (or its intermediates or derivatives) from a solid powder mixture of several chemicals, including chlorinated sucrose; extraction being done by water and the water extract being subjected to a any suitable extraction process including to conventional extraction in any suitable solvent, including ethyl acetate, methanol, methyl ethyl ketone, acetone, which are capable of selective extraction of substantially pure form of chlorinated sucrose free from impurities.

24. Chlorinated sucrose, its intermediates, its derivatives of process of claim 1 to claim 23, at a least part of which is amorphous or non crystalline.

25. Chlorinated sucrose, its intermediates, its derivatives of claim 24 produced by process of claim 1 to 23.

26. Chlorinated sucrose, its intermediates, its derivatives of claim 24 which comprises of :

i) average particle size of 8 micron or less, within a range of 5 micron to 8 micron.

ii) residual moisture content of 10% or less, more particularly less than 5%, still more particularly less than 0.5%.

27. Chlorinated sucrose, its intermediates, its derivatives of chlorinated sucrose, its intermediates, its derivatives, at least a portion of which comprises of particles less than 20 micron precipitated as microcrystalline particles directly from a process of crystallization.

28. Chlorinated sucrose, its intermediates, its derivatives of claim 27 produced by process of claim 1 to 23.

29. Chlorinated sucrose, its intermediates, its derivatives of claim 27 which comprises of:

i) average particle size distribution of 12 micron or less, majority of particles being within a range of 8 micron to 10 micron

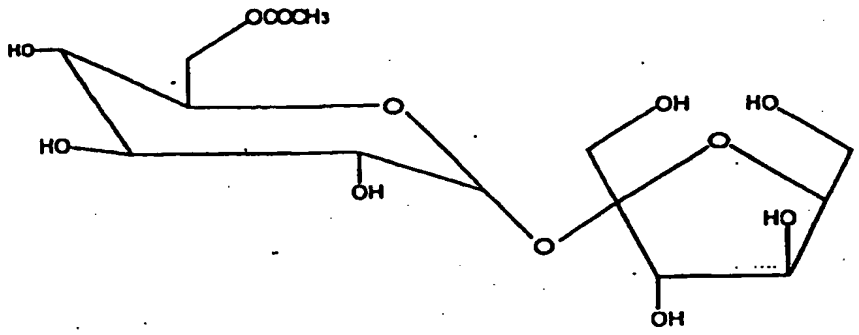
ii) various shapes ranging from globular particles to fully crystallized needles

iii) residual moisture content of 10 % or less, more particularly less than 0.5%, still more particularly less than 0.3%

30. Chlorinated sucrose, its intermediates, its derivatives at least a part of which consists of amorphous or non crystalline or of particles less than 20

micron microcrystalline particles produced directly from a process of crystallization.

31. An oral composition, ingestible as well as non-ingestible including a toothpaste and a chewing gum, a food, a beverage; high intensity sweetener composition; in solid, semi-solid or liquid form, to which is added a composition of chlorinated sucrose of one or more of claim 24, claim 25, claim 26, claim 27, claim 28, claim 29, and claim 30.

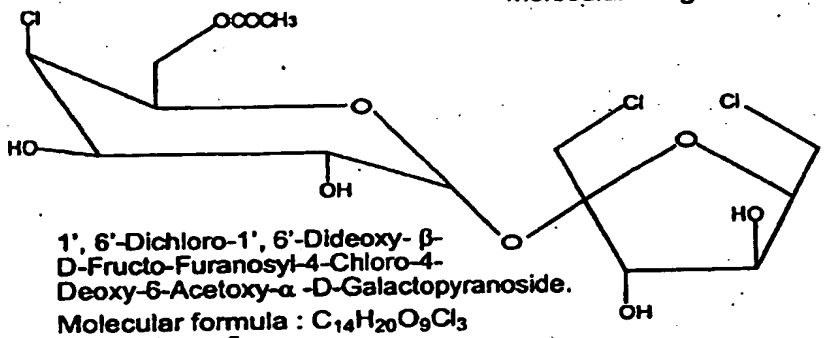


Sucrose - 6 - Acetate

Molecular weight : 384

$POCl_3$ +DMF
115°C

Chlorination

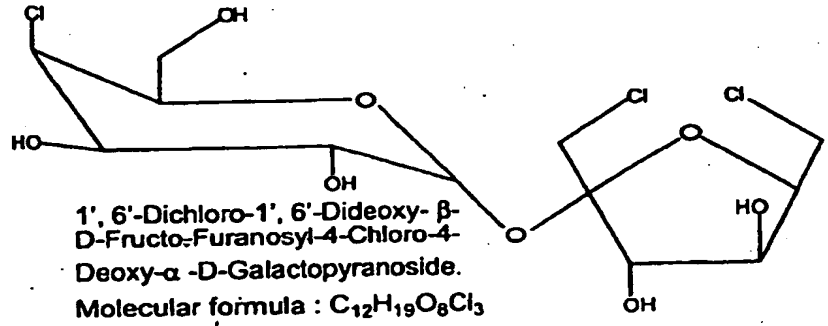


1', 6'-Dichloro-1', 6'-Dideoxy- β-D-Fructo-Furanosyl-4-Chloro-4-Deoxy-6-Acetoxy-α -D-Galactopyranoside.

Molecular formula : $C_{14}H_{20}O_9Cl_3$

Molecular weight : 439.5.

De Acetylation



1', 6'-Dichloro-1', 6'-Dideoxy- β-D-Fructo-Furanosyl-4-Chloro-4-Deoxy-α -D-Galactopyranoside.

Molecular formula : $C_{12}H_{19}O_8Cl_3$

Molecular weight : 397.64

FIG 1

AGITATED THIN FILM DRYER (ATFD)

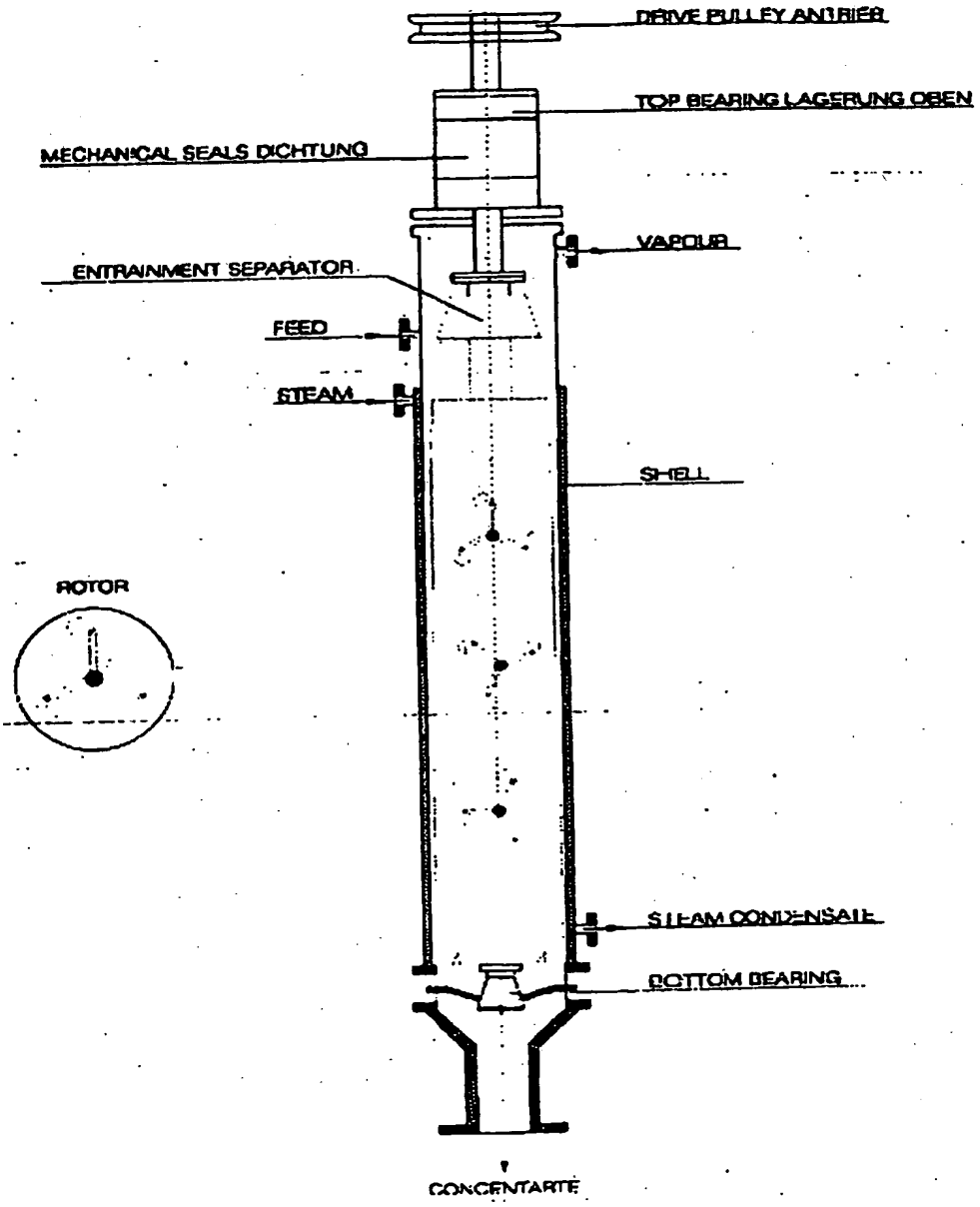


FIG 2

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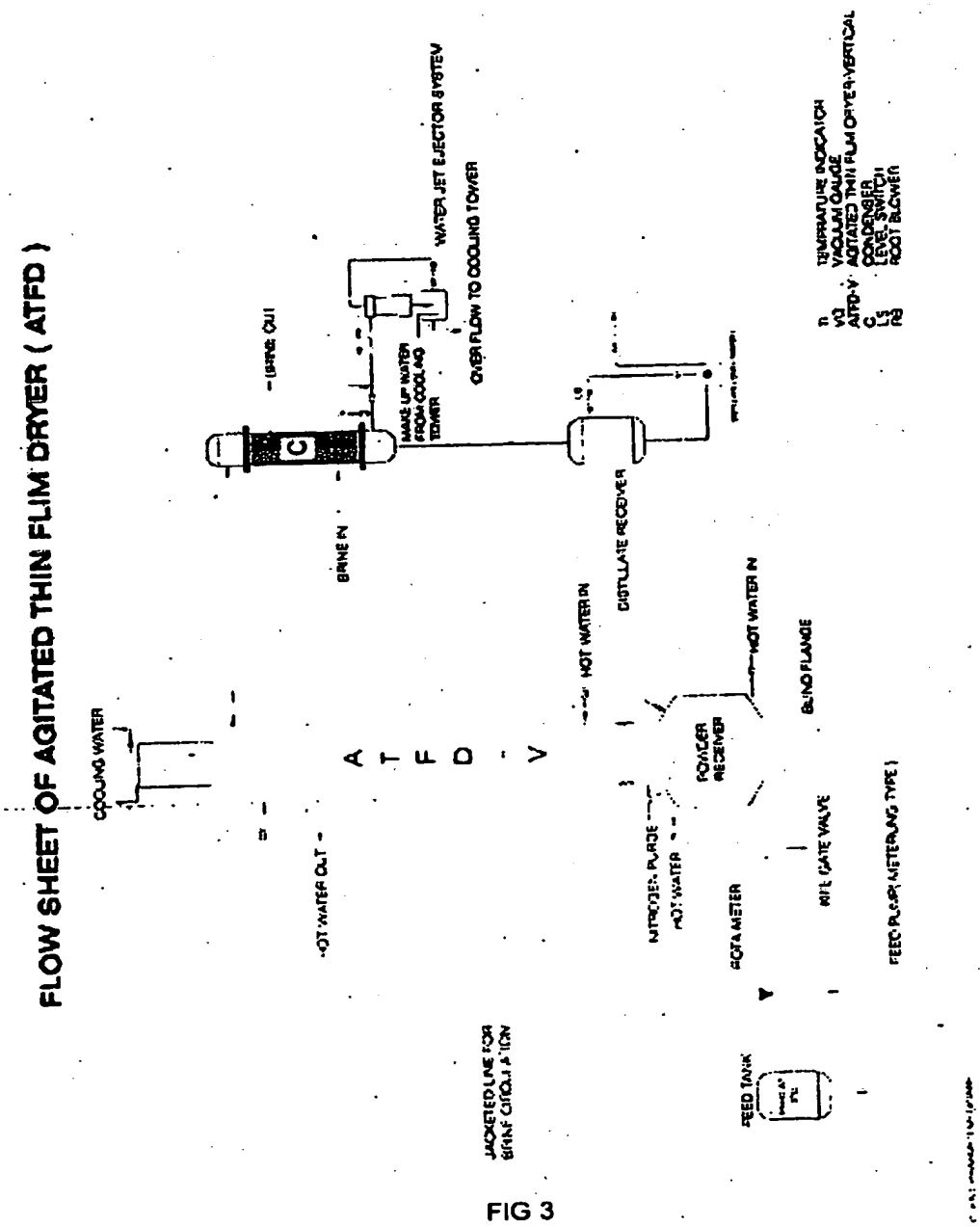

FIG 3

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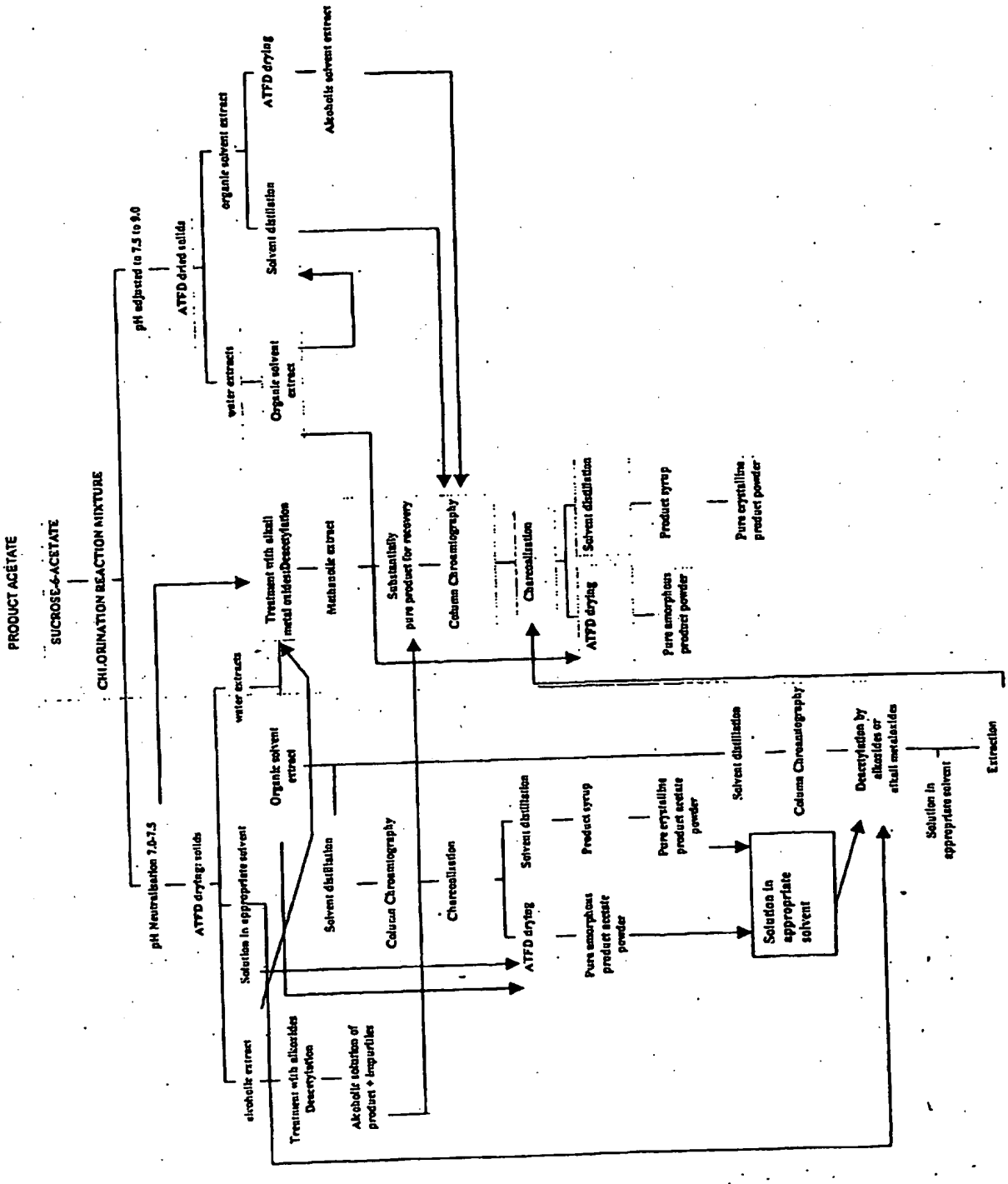

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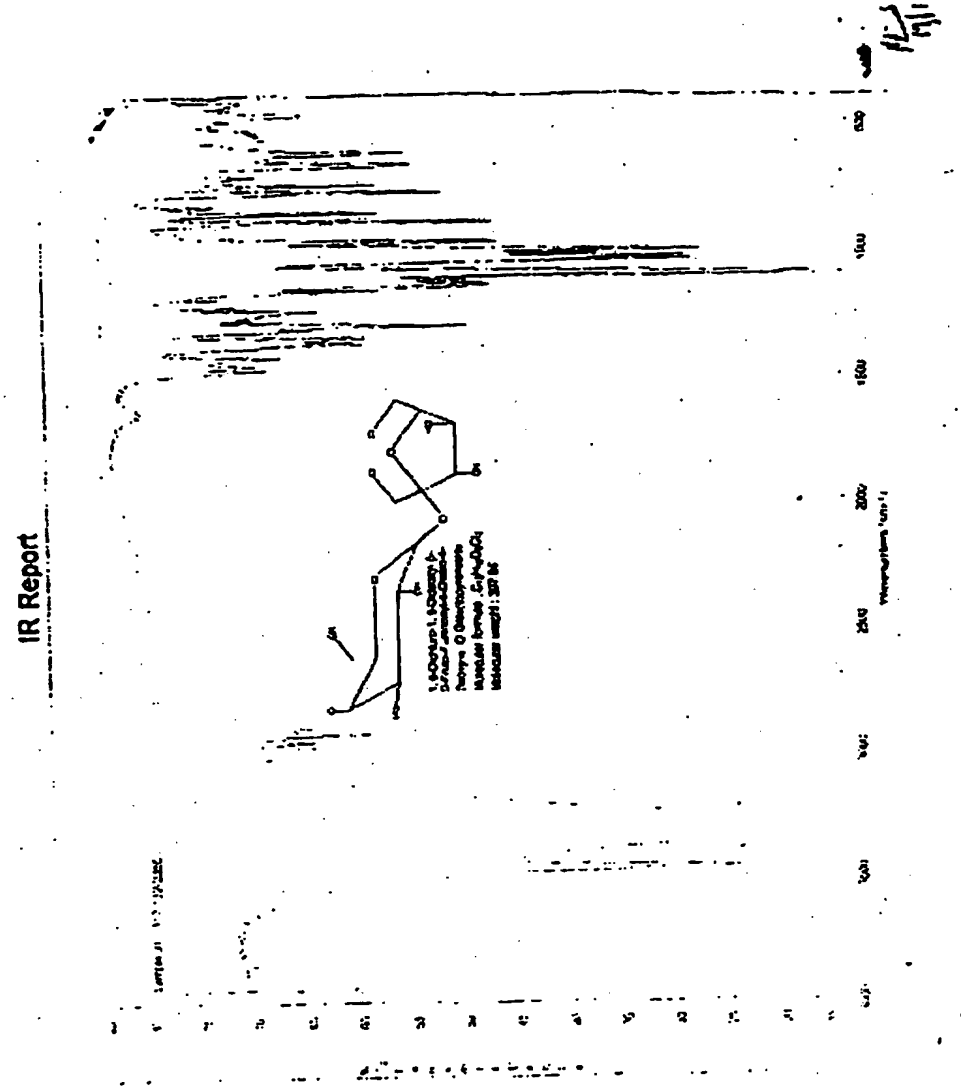

FIG 5

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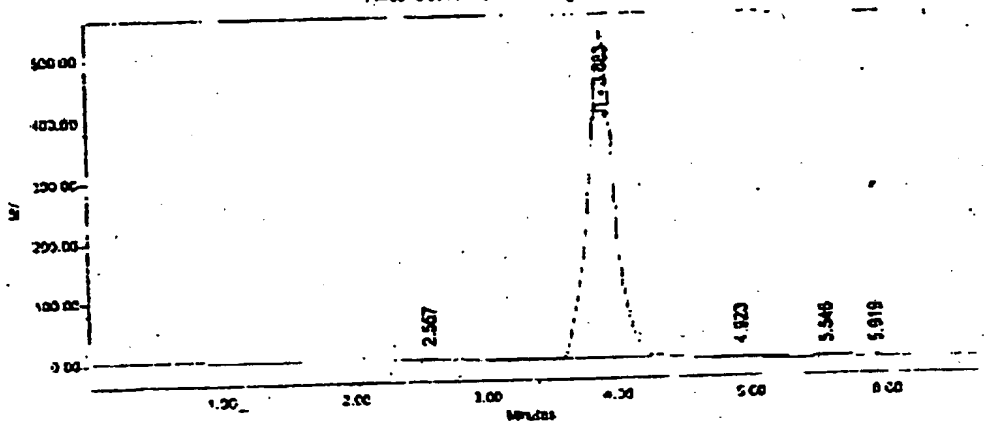
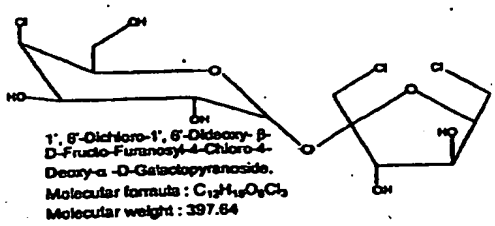
SampleName:	1', 6'-Dichloro-1', 6'-Dideoxy- b- D-Fructo-Furanosyl-4-Chloro-4- Deoxy-a -D-Galactopyranoside.
Vial	1
Injection	4
Injection Volume	10.00 ul
Channel	410
Run Time	8.0 Minutes
Sample Type	Sample
Date Acquired	VB04 10:10:03 AM
Acq Method Set	PHARMED_MTH
Processing Method	PHARMED_PRO
Date Processed	

Auto-Scaled Chromatogram



Peak Results

	Peak Name	RT	Area	Height	% Area	% Height	Id Type
1		2.557	35707	2450	0.51	0.45	BB
2	JJ	3.883	7130944	539348	98.35	98.87	BB
3		4.923	59532	1926	0.82	0.35	BB
4		5.546	9102	833	0.13	0.15	BB
5		5.919	34342	948	0.20	0.17	BB



1', 6'-Dichloro-1', 6'-Dideoxy- β-D-Fructo-Furanosyl-4-Chloro-4-Deoxy-α -D-Galactopyranoside.
Molecular formula : $C_{12}H_{19}O_8Cl_3$
Molecular weight : 397.64

FIG 6

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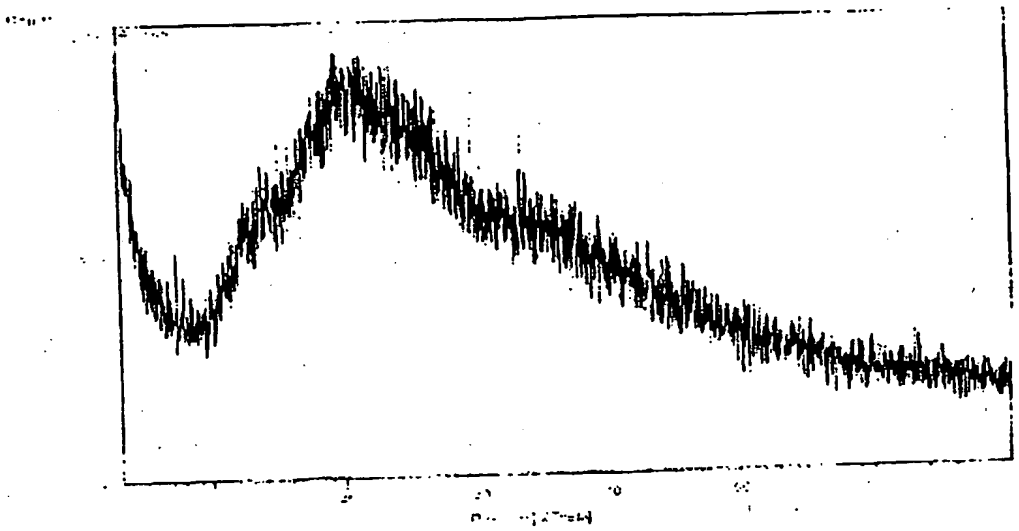

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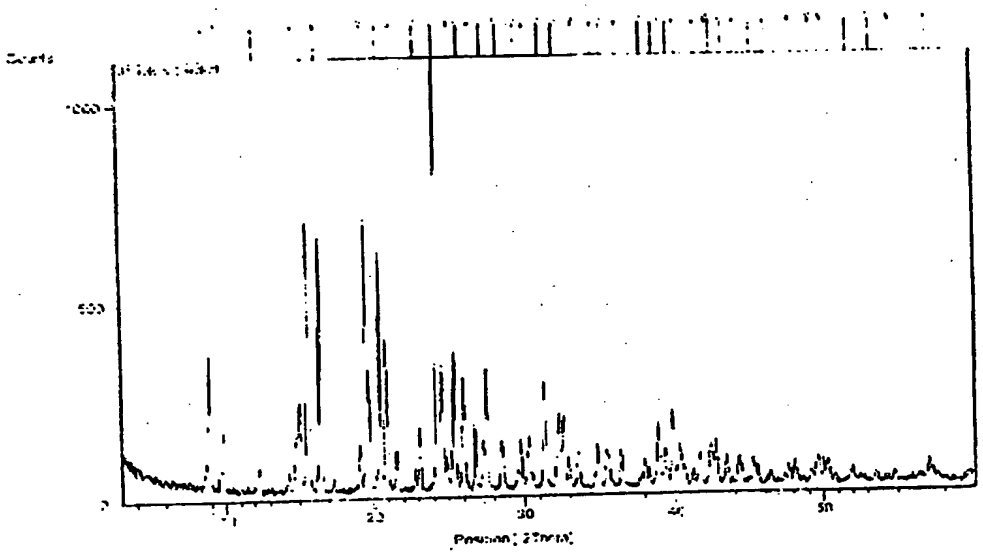

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